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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/604,985	08/29/2003	Itzhak Bentwich	050992(0200CPUS12)	1984

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/604,985	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5 and 7-21* is/are pending in the application.

4a) Of the above claim(s) *1,4 and 10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,7-9 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/06 (1 of 1 and 1 of 12)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 26 October 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 26 July 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 26 October 2006, claims 1, 2, 4, 5, and 7–21 are pending in the application. Claims 1, 4, and 10-16 remain withdrawn.

Claims 2, 5, 7-9, and 17-21 are currently under examination.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112, second paragraph—withdrawn

The rejection of Claims 2, 5, 7-9, and 17-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendments to the claims.

Specification—new

The specification is objected to because the Brief Description of the Drawings at paragraphs 58 and 59, pages 25 and 26, refers to Figs. 24A through 1699D and Figs. 1700 to 1706. No such figures are found in the instant application. A review of the drawings filed with the original application finds only Figs. 1-23.

Clarification and correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

With the amendment of 10/26/06, Claim 19 reads as follows: "An isolated nucleic acid with a sequence complementary to the nucleic acid sequence of SEQ ID NO: 1, wherein the nucleic acid is from about 91 to 120 nucleotides."

The amendment to the claims submitted on 10/26/06 introduces the limitation "wherein the nucleic acid is from about 91 to 120 nucleotides."

A review of the instant application, which is over 13,000 pages long, fails to find clear antecedent support for the instant limitation.

MPEP 2163, Section II, Part A, states in part that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims.

In a previous amendment to claim 1, submitted on 6/23/06, Applicant stated that support for that amendment "about 91 to about 120 nucleotides" could be found at paragraph 11 of the specification. However, paragraph 11 does not provide implicit, explicit, or inherent support for this size limitation in a DNA complement of SEQ ID NO:1 or for the RNAs encoded by SEQ ID NO:1. The size range explicitly stated is from about 50 to about 120 nucleotides (see paragr. 11).

Thus, in the instant case, Applicant has not pointed out where the amended claim is supported, nor does there appear to be a written description of the claim limitation in the application as filed (MPEP 2164.04). Accordingly, a review of the application fails to find clear, antecedent support for the instant limitation in claim 19.

Accordingly, the instant claim as a whole is rejected for lack of written description support.

Claim Rejections - 35 USC § 101 and 112, First Paragraph—new

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 5, 7-9, and 17-21 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility.

The claims are drawn to an isolated RNA of about 18 to 24, 50 to 77, or about 22 nucleotides encoded by a nucleic acid comprising the sequence of SEQ ID NO: 1. Also claimed are complements to said isolated RNA and an isolated nucleic acid sequence complementary to the sequence of SEQ ID NO:1, wherein the sequence is from about 91 to 120 nucleotides.

A review of the sequence listing, which comprises 97,967 sequences, finds that SEQ ID NO:1 corresponds to a 131-nucleotide DNA.

A review of the specification, which is nearly 14,000 pages long, finds general assertions and statements that the present invention relates to a group of bioinformatically detectable novel genes, which Applicant refers to as "genomic address messenger" or "GAM" genes, which are believed to be related to the micro RNA (miRNA) group of genes.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification makes general statements that the bioinformatically detectable sequences, GAMs, and the miRNAs they may encode may have utility for regulating target genes and possibly for treating disease.

However, the specification provides no direct or indirect evidence for any specific, substantial, or credible utility of the instantly claimed RNAs encoded by SEQ ID NO:1. There is no disclosure indicating or suggesting that SEQ ID NO:1 has itself ever been isolated or examined in any way, nor any evidence that the claimed RNA has, in fact, been isolated or prepared or studied or examined under any conditions. Any asserted utility for the claimed sequences appears to be merely speculation based on "bioinformatics," homology, and secondary structure predictions suggesting that the encoded RNAs are miRNAs because they have a miRNA-like hairpin structure and some degree of sequence homology to some unidentified target sequence. On this basis, and since other miRNAs are known to have gene expression modulating properties, Applicant appears to be asserting that the bioinformatically detectables sequences, or GAMs, such as the RNAs encoded by SEQ ID NO:1 also have utility.

However, that utility has not been clearly defined, nor does the prior art search of SEQ ID NO:1 provide any substantial evidence to show that the RNAs of the size now claimed have any substantial, specific, or credible utility.

Applicant has not shown, and there is no evidence in the prior art to suggest, that the RNAs now claimed are expressed in any cell whatsoever. While there may be some purported links or sequence homology connections between the instantly claimed sequences and RNAs to known gene, which may have a utility, Applicant has not pointed or directed the Examiner to those portions of the 14,000 pages of specification, drawings, and sequence disclosures that might substantiate a utility.

Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequence. That is, no evidence can be found verifying or even suggesting that SEQ ID NO:1 actually gives rise to miRNAs in any cell or organism, and if it does, Applicant has not described or shown any specific, substantial, or credible utility for the

expressed miRNA. The fact that an miRNA can regulate gene expression is not specific or substantial because 1) this activity is inherent to almost any miRNA, and 2) because Applicant has not taught any use or purpose for the inhibitory activity nor proposed any specific utility for the asserted down regulation of the target gene of the RNA now claimed.

For instance, Applicant has not provided evidence that the RNAs encoded by instant SEQ ID NO: 1 play any role in the predisposition of humans or other mammals to disease. There is no evidence to suggest that the miRNAs or RNAs purportedly expressed by SEQ ID NO:1 are up or down regulated in response to foreign agents or disease states or that the expression or targeting of miRNAs of the instant invention would provide any real world information for a specific use other than general knowledge as to understanding the biological function of the miRNA.

The specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and disease and disease diagnosis and prevention purposes, and for monitoring disease progress.

However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the specification does not disclose any specific function for SEQ ID NO:1, aside from indicating that it may encode an miRNA, it is unclear how or why one of skill in the art would use the information obtained by

measuring SEQ ID NO:1 or its DNA complements or expressed RNAs for any particular purpose aside from general research. Further, since Applicant does not identify whether abnormal SEQ ID NO:1 expression is causally related to any disease or condition, or whether abnormal SEQ ID NO:55663 function (e.g., a polymorphism) predisposes anyone to any disease or condition, the only recognizable utility of diagnostic probes is as tools for scientific research, and with no indication that anything useful will be discovered. Therefore, the asserted utility is not substantial since the application provides no teaching regarding how to use the probes or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO:1, much less the claimed RNA equivalents thereof have any specific biological function. No evidence or information is found either in the specification or the prior art linking SEQ ID NO:1 or its RNA with the modulation of any bacterial or mammalian gene or with the conditions that render cells or hosts susceptible to any disease or disorder, for example. No convincing evidence is found teaching any biological function for SEQ ID NO:1 at all. In fact, no evidence

is found suggesting or stating that the RNAs encoded by SEQ ID NO:1 have been made, isolated, cloned, detected, expressed, or even analyzed in any living cell *in vitro* or *in vivo.*

In summary, no biological or biochemical function has been assigned to the claimed RNAs encoded by SEQ ID NO:1, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to an miRNA and have some direct or indirect relation to human biology and/or cell function.

Thus, the proposed utility of the RNAs encoded by SEQ ID NO:1 as a therapeutic target or agent, a research tool, material resource for preparing diagnostic probes, vectors, a host cells, are simply starting points for further research and investigation into potential practical uses of the claimed polynucleotide.

> Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)
>
> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> ...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific, substantial, or credible utility for SEQ ID NO:1 or the RNAs it encodes, much less any of the RNA or DNA complements of these sequences. No target gene has been conclusively identified nor has any evidence been presented linking SEQ ID NO:1 or the RNA encoded by SEQ ID NO:1 with any target gene, nor any evidence showing or suggesting that any small RNAs are expressed by SEQ ID NO:1 in any cell,

and, if so, what function these small RNAs perform. A credible, specific, and substantial nexus has not been established.

***

Claims 2, 5, 7-9, and 17-21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
November 16, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635